

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/55, 31/495, 31/47, 9/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/23222</b> <b>(43) International Publication Date:</b> 3 July 1997 (03.07.97)
<b>(21) International Application Number:</b> PCT/US96/20197 <b>(22) International Filing Date:</b> 20 December 1996 (20.12.96)  <b>(30) Priority Data:</b> 60/009,351 21 December 1995 (21.12.95) US  <b>(71) Applicant (for all designated States except US):</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KAPIN, Michael, A. [US/US]; 3602 Silkwood Trail, Arlington, TX 76016 (US). DESANTIS, Louis, M., Jr. [US/US]; 2316 Winton Terrace West, Fort Worth, TX 76109 (US).  <b>(74) Agents:</b> COPELAND, Barry, L. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, CA, CN, JP, KR, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> USE OF CERTAIN ISOQUINOLINESULFONYL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA AND OCULAR ISCHEMIA  <b>(57) Abstract</b> <p>Isoquinolinesulfonyl compounds are used in ophthalmic compositions to treat glaucoma or other ischemic-borne ocular disorders such as retinopathies or optic neuropathies. These compounds vasodilate ocular blood vessels, lower IOP and prevent or reduce the progression of visual field loss.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## USE OF CERTAIN ISOQUINOLINESULFONYL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA AND OCULAR ISCHEMIA

### Background of the Invention

The present invention relates generally to the field of ophthalmology. In particular, the invention relates to the treatment of ocular disorders including visual field loss and glaucoma using a isoquinolinesulfonyl compound, which lowers intraocular pressure (IOP) and produces dilation of ocular blood vessels.

Although the underlying causes of glaucoma are not fully understood at this time, glaucoma is characterized by damage to the optic nerve head, accompanied by a decrease in the normal visual field. One risk factor for glaucomatous visual field loss is elevated IOP. In fact, glaucoma has historically been treated by drug and/or surgical therapy to lower elevated IOP. While elevated IOP has been positively correlated with the rate of progression of visual field loss in glaucoma, visual field loss may occur at levels of IOP which are considered within the normal range. Thus, other factors, alone or in addition to elevated IOP, may influence the occurrence and rate of progression of visual field loss.

To remain healthy and function normally, the retina and the optic nerve head fibers (neurons) must receive a proper supply of nutrients and oxygen, and must have their carbon dioxide and other metabolic waste products removed. This is accomplished by the microcirculation in these tissues. As used herein, the term "microcirculation" refers to the blood flow through the nutritive blood vessels, across whose walls nutrients, gases and waste products move. Blood flow to the eye depends upon the perfusion pressure (the systemic blood pressure minus the IOP). Some tissues have the ability to maintain (i.e., autoregulate) blood flow through a range of perfusion pressures such that an increase in systemic blood pressure may cause a reduction in the caliber of the blood vessel lumen. Conversely, reduction in systemic pressure in such tissues can result in vessel dilation;

however, there is a point where perfusion pressure falls to such a level that the vessel is maximally dilated. Any further fall in perfusion pressure results in a reduction of blood flow to the tissue (ischemia). Ischemia may also result from obstruction, vasospasm, increased vascular resistance, or other interference with microcirculation. Prolonged ischemia ultimately can result in tissue necrosis or neuronal cellular apoptosis. In the case of the optic nerve head or retina, a state of visual dysfunction may precede the death of the neurons. Hence, if ischemia is involved in the death of optic nerve fibers due to glaucoma or some other ischemic-borne retinopathies or optic neuropathies, then its prevention could protect the neurons from death or loss of function.

The vasodilatory and spasmolytic activities of certain isoquinolinesulfonyl compounds have been described with respect to non-ocular tissues. See, e.g., EP 0 187 371 B1, which corresponds to U.S. Patent No. 4,678,783. These vascular attributes are likely associated with inhibition of myosin-light chain kinase activity. Myosin-light chain kinase is an enzyme necessary for the excitation-contraction coupling of contractile activity in vascular smooth muscle. Inhibition of this enzyme results in vascular smooth muscle relaxation (i.e., vasodilation) which can produce an increased blood flow.

#### Summary of the Invention

The inventors believe that microcirculatory disturbances that restrict nutritive blood flow to the choroid, retina and optic nerve head are likely involved in the progression of visual field loss. While bound by no theories, the inventors postulate that compounds which enhance oxygen and nutrient delivery by enhancing ocular blood flow may be beneficial in preventing optic nerve head injury and may subsequently prevent or alter the rate of progression of visual field loss associated with glaucoma and ischemic optic neuropathies.

The present invention provides compositions and methods useful in the treatment of glaucoma (with or without ocular hypertension) and ocular ischemia, which may result in retinopathies and optic neuropathies. The compositions contain an isoquinolinesulfonyl

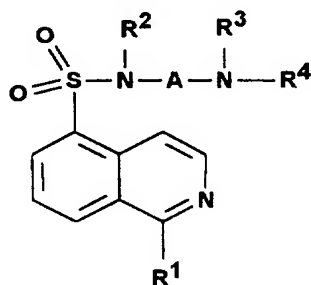
compound which is effective in reducing or preventing optic nerve head or retinal damage as well as reducing IOP toward normal levels and thus, in reducing or preventing visual field loss.

In an alternative embodiment of the compositions and methods of the present invention, the above compositions may further include a mucomimetic polymer, a gelling polysaccharide, a finely divided drug carrier substrate (defined below), or a combination of these components. These additional components provide compositions which enhance comfort and provide sustained release and delivery of the drug to the eye.

#### Detailed Description of the Invention

Elevation of IOP is associated with clinical manifestations characteristic of glaucomatous optic neuropathy. Optic nerve dysfunction may be the result of pressure-induced changes in the structure of the optic nerve head and/or reduced circulation to the optic nerve head and retina. In addition to affecting vascular resistance and blood flow, the inventors have discovered that certain isoquinolinesulfonyl compounds also lower intraocular pressure.

The isoquinolinesulfonyl compounds of the present invention are the compounds of formula (I) shown below, as well as their pharmaceutically acceptable salts.



(I)

wherein  $R^1$  represents a hydrogen atom, a chlorine atom or a hydroxyl group; and when  $R^1$  represents a hydrogen atom,

A represents an ethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms, a phenyl group or a benzyl group,  $R^2$  and  $R^3$  are directly bonded with each other, thereby forming a trimethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms, a phenyl group or a benzyl group, and  $R^4$  represents a hydrogen atom or an alkyl group having 1 to 6 carbon atoms; and

when  $R^1$  represents a chlorine atom or a hydroxyl group,

A represents an alkylene group having 2 to 6 carbon atoms, said group being unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms,

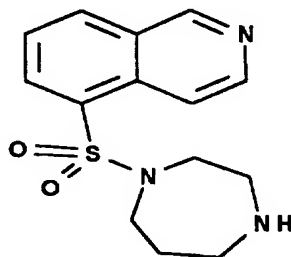
$R^2$  and  $R^3$  are not bonded with each other and each independently represent a hydrogen

atom or an alkyl group having 1 to 6 carbon atoms, or  $R^2$  and  $R^3$  are directly bonded with each other, thereby forming an ethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms or a trimethylene group unsubstituted or substituted with alkyl group having 1 to 6 carbon atoms, and

$R^4$  represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or an amidino group;

and pharmaceutically acceptable salts thereof. With respect to the above-mentioned alkyl groups, they may be a straight chain group or a branched chain group. These compounds and methods of their syntheses are disclosed in U.S. Patent No 4,678,783, the entire contents of which are incorporated herein by this reference. Other isoquinolinesulfonyl derivatives and methods of their syntheses are disclosed in U.S. Patent No. 4,525,589, the entire contents of which are likewise incorporated herein by this reference.

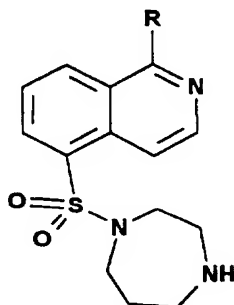
The preferred isoquinolinesulfonyl compound of the present invention is hexahydro-1-(5-isoquinolinylsulfonyl)-1H-1,4-diazepine, also known as 1-(5-isoquinolinesulfonyl)-homopiperazine, and shown below as Compound (II), as well as its pharmaceutically acceptable salts.



(II)

Most preferred is the hydrochloride salt of Compound (II). The hydrochloride salt of Compound (II), known as fasudil, AT-877, and HA-1077 is manufactured by Asahi Chemical Industry Co., Ltd. (Japan).

Alternatively, Compound (II) and a preferred metabolite thereof may be represented by the following formula:



(III)

wherein R = H or OH.

In general, for topical administration an amount of an isoquinolinesulfonyl compound between about 0.001 and about 10.0 percent by weight (wt%) is used in the

compositions of the present invention. It is preferred that between about 0.01 and about 3.0 wt% is used, and it is especially preferred to use an amount between about 0.1 and about 2.0 wt%.

The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Patent No. 4,911,920 issued March 27, 1990 and in U.S. Patent No. 5,212,162 issued May 18, 1993. The entire contents of these two patents are incorporated herein by reference. For purposes of this invention, the term "mucomimetic polymers" includes carbomers (discussed below), mucopolysaccharides (e.g. hyaluronic acid and chondroitin sulfate) and cellulosic polymers (e.g. methyl cellulose, hydroxy propyl methyl cellulose, hydroxyethyl cellulose, carboxy methyl cellulose, and hydroxy propyl cellulose).

The preferred mucomimetic polymers useful in the present invention are anionic and have a molecular weight between about 50,000 and 6 million daltons. These preferred polymers are characterized as having carboxylic acid functional groups and preferably contain between 2 and 7 carbon atoms per functional group. The gels which form during preparation of the ophthalmic polymer dispersion have a viscosity between about 1,000 to about 300,000 centipoise (cps). Suitable polymers are carboxy vinyl polymers, preferably those called carbomers, e.g., CARBOPOL® (Goodrich Co., Cleveland, Ohio). Specifically preferred are CARBOPOL® 934 and 940. Such polymers will typically be employed in an amount between about 0.05 and about 8.0 wt%, depending on the desired viscosity of the composition. Pourable liquid compositions generally comprise an amount of the polymer between about 0.05 and about 2.0 wt%.

As used herein, the term "finely-divided drug carrier substrate" (or "DCS") means finely-divided solids, colloidal particles, or soluble polymers and/or polyelectrolytes which are capable of selective adsorption or binding with drug molecules. Examples of DCS



include, but are not limited to: finely divided silica, such as fumed silica, silicates and bentonites; ion exchange resins, which can be anionic, cationic or non-ionic in nature; and soluble polymers, such as, alginic acid, pectin, soluble carrageenans, CARBOPOL®, and polystyrene sulfonic acid. In general, the DCS component is used at a level in the range of about 0.05 to about 10.0 wt%. For particulate DCS, the average particle size diameter ranges from about 1 to about 20 microns. The amount of DCS and its characteristics (e.g., amount of cross-linking, particle size) may be varied in order to produce the desired time-release profile for the chosen drug.

Preferred DCS are the ion exchange resins. Some resins which are used in chromatography make ideal DCS for binding drugs in the compositions of the present invention. Such resins are readily available, for example, from Rohm & Haas (Philadelphia, Pennsylvania) under the name AMBERLITE® and from Dow Chemical Co. (Midland, Michigan) under the name DOWEX®. The average particle size diameter of the commercially available forms of the resins is about 40 to about 150 microns. Such commercially available particles are most conveniently reduced to a particle size range of about 1.0 to about 25 microns by ball milling, according to known techniques. At least 95% of the resulting spheroidal particles will preferably have a diameter less than 20 microns. The ion exchange resins will typically be present in an amount between about 0.05 and about 10.0 wt% and will have an average particle size diameter between about 1 and about 20 microns.

In addition to the above-described principal ingredients, the compositions of the present invention may further comprise various formulatory ingredients, such as antimicrobial preservatives and tonicity agents. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium 1 and other agents equally well-known to those skilled in the art. Such preservatives, if utilized, will typically be employed in an amount between about 0.001 and about 1.0 wt%. Examples of suitable agents which may be utilized to adjust the tonicity or osmolality of the

formulations include: sodium chloride, potassium chloride, mannitol, dextrose, glycerin and propylene glycol. Such agents, if utilized, will typically be employed in an amount between about 0.1 and about 10.0 wt%.

As will be appreciated by those skilled in the art, the compositions may be formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels and erodible solid ocular inserts. The compositions are preferably aqueous, have a pH between about 3.5 and about 8.0 and an osmolality between about 280 and about 320 milliOsmoles per kilogram (mOsm/kg).

The compositions of the present invention may also comprise non-aqueous formulations such as: substantially non-aqueous liquids, substantially non-aqueous semi-solid compositions, and solid compositions or devices. The first class, substantially non-aqueous liquids, includes a isoquinolinesulfonyl compound dissolved or suspended in one or more of the following: vegetable and mineral oils, such as liquid petrolatum, corn oil, castor oil, sesame oil, and peanut oil; triglycerides, such as the capric/caprylic triglycerides commonly used in foods and cosmetics; liquid lanolin and lanolin derivatives; and perfluorohydrocarbons. The second class, semi-solid compositions, comprises an isoquinolinesulfonyl compound dissolved or suspended in one or more of the following: various types of petrolatum, such as white, yellow, red, and so on; lanolin and lanolin derivatives; gelled mineral oil having a hydrocarbon base, such as PLASTIBASE®; petrolatum and ethylene carbonate mixtures; petrolatum in combination with surfactants and polyglycol, such as polyoxyl 40 stearate and polyethylene glycol.

The third class, solid compositions or devices, includes an isoquinolinesulfonyl compound in association with (i) non-erodible devices which are inserted into the conjunctival sac of the eye and later removed, such as the Alza-type diffusion or osmotic pressure controlled polymer membranes; and (ii) bioerodible polymers which do not have to be removed from the conjunctival sac, such as essentially anhydrous but water soluble polymers and resins (e.g., celluloses, polycarboxylic acids, and so on). Especially preferred

are the bioerodible inserts described and detailed in U.S. 4,540,408 (Lloyd) and U.S. 4,730,013 (Bondi et al.), wherein isoquinolinesulfonyl compounds of the present invention would be entrained in a non-aqueous matrix consisting essentially of polyvinyl alcohol. The entire contents of these two patents are incorporated herein by reference.

As will further be appreciated by those skilled in the art, the isoquinolinesulfonyl compounds of the present invention may also be administered intraocularly, periocularly or systemically (e.g. parenterally or orally).

Intraocular or periocular administration may be effected by incorporating a isoquinolinesulfonyl compound in a surgical irrigating solution used in ophthalmic surgery, or, preferably, by intravitreal or periocular injection. Such injection therapy will typically require from about 0.1 nM to about 1mM (approximately 0.02ng to 500µg) of a isoquinolinesulfonyl compound for each eye treated. It is preferred that between about 200nM and about 160µM (approximately 40ng to 80µg) per eye be used in such therapy.

The preferred routes of systemic administration are oral and intravenous. Oral dosing of an isoquinolinesulfonyl compound in accordance with this invention will typically range from about 1.0 to about 1000 mg, one to four times per day. The preferred dosing range of oral administration is from about 10 to about 250 mg two to three times per day. Intravenous dosing of an isoquinolinesulfonyl compound in accordance with this invention will typically range from about 0.01 to about 100 mg, one to four times per day. The preferred dosing range for intravenous administration is from about 1.0 to about 30 mg, two to three times per day.

The present invention is also directed to methods of treating glaucoma and other ophthalmic diseases and abnormalities associated with visual field loss. The treatment may be effected by administering a therapeutically effective amount of an isoquinolinesulfonyl compound topically, intraocularly, periocularly or systemically. The preferred methods comprise topically applying to the affected eye(s) of the patient a therapeutically effective

amount of a composition according to the present invention. The frequency and amount of dosage will be determined by the clinician based on various clinical factors. The preferred methods will typically comprise topical application of one or two drops (or an equivalent amount of a solid or semi-solid dosage form) to the affected eye as needed, preferably one to three times per day.

The following examples are presented to further illustrate various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

#### Example 1

The hydrochloride salt of Compound II, also known as fasudil hydrochloride or just fasudil, was topically administered to eyes of ocular hypertensive monkeys, New Zealand Albino (NZA) and Dutch Belted (DB) rabbits. The results are presented in Table 1. As presented, Compound II effectively lowered IOP in both ocular normotensive and hypotensive (laser-induced) primates. In NZA rabbits, IOP was markedly lowered below base line for the four hour dose response. Compound II also lowered IOP in the DB rabbit; however, the reduction in IOP was not sustained as in the NZA rabbit study.

Table 1.

**EFFECT OF FASUDIL ON IOP REDUCTION IN THE OCULAR  
HYPERTENSIVE AND NORMOTENSIVE MONKEY, NEW  
ZEALAND ALBINO AND DUTCH BELTED RABBIT**

ANIMAL MODEL	Baseline IOP (mmHg)	PERCENT CHANGE FROM BASELINE				
		1 HR	2 HR	3 HR	4 HR	6 HR
Lasered MIOP (n=9) †	32.1±3.2	21.9±6.7 ↓	--	14.6±6.5 ↓	--	23.4±4.4 ↓
Lasered MIOP (n=9)	38.2±3.3	15.9±6.8 ↓	--	16.1±4.8 ↓	--	7.1±4.9 ↓
Normal MIOP (n=9)	20.4±1.4	18.9±5.5 ↓	--	21.7±5.2 ↓	--	11.1±5.3 ↓
Dutch Belted Rabbit (n=7) ††	37.4±0.6	33.7±2.1 ↓	18.0±3.7 ↓	10.8±5.2 ↓	6.6±3.9 ↓	--
Dutch Belted Rabbit (n=7) ††	32.1±0.4	33.1±2.7 ↓	25.2±3.5 ↓	16.7±3.9 ↓	11.7±4.0 ↓	--
NZA Rabbit (n=7) ††	27.2±0.3	36.2±3.7 ↓	35.5±3.6 ↓	26.1±3.9 ↓	22.5±3.8 ↓	--

All drugs were administered to eyes in a topical manner at a dose = 500 µg (2x25 µl). Fasudil was formulated in phosphate buffered saline containing 0.01% benzalkonium chloride.  
 † No significant change in IOP from baseline values was observed in the contralateral untreated ocular normotensive eye or in a vehicle treated ocular hypertensive eye. †† No significant change in IOP from baseline values were observed in the contralateral untreated eye.  
 MIOP = monkey intraocular pressure. n = number of animals in study.

Example 2

Compound II (hydrochloride) was administered topically to the eyes of Dutch Belted (DB) rabbits in doses of 75 and 150µg. The results are presented in Table 2.

Table 2.

**DOSE-RESPONSE STUDIES OF FASUDIL ON IOP IN THE DUTCH BELTED RABBIT**

Compound	Baseline IOP (mmHg)	Percent Change from Baseline				
		0.5 hr	1 hr	2 hr	3 hr	4 hr
Group 1 Fasudil 150 µg OD	33.0±0.8	8.8±3.8 ↓	11.5±3.2 ↓	14.6±3.5 ↓	3.4±2.7 ↓	0.5±3.2 ↑
Group 1 Vehicle OS	33.8±0.6	3.5±1.9 ↓	3.7±2.4 ↓	5.7±2.6 ↓	0±2.4 ↓	2.1±3.2 ↑
Group 2 Fasudil 75 µg OD	34.3±0.8	3.2±2.8 ↓	3.3±1.9 ↓	1.7±2.7 ↓	5.2±2.2 ↓	2.9±2.1 ↓
Group 2 Vehicle OS	33.8±0.6	1.1±0.6 ↑	5.9±2.6 ↑	6.0±3.9 ↑	4.5±1.9 ↑	1.9±3.4 ↑

All drugs were administered to eyes in a topical manner (1x30 µl). All compounds were formulated in a phosphate buffered saline containing 0.01% benzalkonium chloride. N=6 animals/group; OD= drug treated eye; OS=vehicle treated contralateral eye.

**Example 3**

A dose study similar to that described in Example 2 was conducted with the NZA rabbit. Compound II (hydrochloride) was administered in a topical ocular fashion in doses of 50, 125 and 250µg. The results of this study are presented in Table 3.

Table 3.

**DOSE-RESPONSE STUDIES OF FASUDIL ON IOP IN THE NEW ZEALAND ALBINO RABBIT**

Compound	Baseline IOP (mmHg)	Percent Change from Baseline				
		0.5 hr	1 hr	2 hr	3 hr	4 hr
Group 1 Fasudil 250 µg OD	20.6±0.3	5.5±6.7 ↓	21.1±5.4 ↓	24.9±6.1 ↓	25.1±4.1 ↓	16.3±4.0 ↓
Group 2 Vehicle OS	21.2±.5	1.1±3.7 ↓	4.4±3.4 ↑	2.7±3.2 ↑	2.7±3.9 ↑	5.4±3.6 ↑
Group 2 Fasudil 125 µg OD	20.4±.7	2.8±3.8 ↑	11.6±2.9 ↓	11.0±4.7 ↓	7.0±4.8 ↓	5.1±2.7 ↓
Group 2 Vehicle OS	21.3±.6	5.3±2.6 ↑	8.3±6.0 ↑	7.3±4.6 ↑	7.2±5.3 ↑	17.1±6.5 ↑
Group 3 Fasudil 50 µg	21.3±.5	1.6±3.0 ↓	3.2±3.1 ↑	2.1±4.7 ↑	1.7±4.3 ↓	10.8±5.7 ↑
Group 3 Vehicle OS	21.4±.8	6.7±4.1 ↑	9.1±1.7 ↑	3.6±3.3 ↑	9.8±7.6 ↑	7.4±4.5 ↑

All drugs were administered to eyes in a topical manner (1x30 µl). All compounds were formulated in a phosphate buffered saline containing 0.01% benzalkonium chloride. N=6 animals/group; OD= drug treated eye; OS=vehicle treated contralateral eye.

**Example 4**

The effect of repeated doses of Compound II on the magnitude and duration of IOP reduction was evaluated in ocular normotensive monkeys. As shown in Table 4, a total of 900µg of Compound II (hydrochloride) administered in three doses, ten minutes apart, resulted in significant IOP reduction.

Table 4.

**EFFECT OF REPEATED DOSES OF FASUDIL ON IOP IN THE OCULAR  
NORMOTENSIVE CYNOMOLGUS MONKEY**

Compound	Baseline IOP (mmHg)	Percent Change from Baseline		
		1 hr	3 hr	5 hr
Fasudil 900 µg OS	20.6±0.8	23.1±2.8 ↓	23.1±3.3 ↓	19.3±3.2 ↓
Vehicle 3 x 30 µl OS	20.2±0.8	4.1±1.8 ↓	0.3±4.4 ↑	1.1±3.7 ↓

Fasudil was administered 3 x 30 µl topically (1 x 30 µl, 10 minutes apart). N=10 for drug treated and N=5 for vehicle. Fasudil was formulated in a phosphate buffered saline containing 0.01% benzalkonium chloride.

Example 5

Topical Ophthalmic Formulation

Ingredient	% (w/v)
Compound II (hydrochloride)	1.5
Benzalkonium chloride	0.01
Phosphate buffered saline	q.s. to 100



Example 6

## Topical Ophthalmic Formulation With Sustained Release

Ingredient	% (w/v)
Compound II (hydrochloride)	1.0
Carbomer 934P or Carbomer 974P	0.5
NaCl	0.4
Mannitol	2.4
Disodium edetate	0.01
BAC	0.01
Water for Injection	q.s. to 100
NaOH or HCl to adjust pH	q.s.

Example 7

## Systemic Formulation (Oral)

Ingredient	Weight Proportion
Compound II (hydrochloride)	50
Sodium Citrate	20
Alginic Acid	5
Polyvinylpyrrolidone	15
Magnesium Stearate	5

Preparation: The dry composition is thoroughly blended, tablets are punched from the resulting mixture, each tablet being of such size that it contains 10mg of Compound II (hydrochloride).

**Example 8**

**Intraocular or Periocular Formulation**  
**(For Intravitreal for Periocular Injection)**

<b>Ingredient</b>	<b>% (w/v)</b>
<b>Compound II (hydrochloride)</b>	<b>0.002</b>
<b>Sterile balanced salt solution</b>	<b>q.s. to 100</b>

**Example 9**

**Method of Treatment (Topical)**

A patient suffering from elevated IOP and/or visual field loss is treated by the topical administration of the formulation of Example 5. One 30 $\mu$ l drop of the formulation is administered one to four times per day to the affected eye(s) thereby reducing the IOP and/or the progression of visual field loss.

**Example 10**

**Method of Treatment (Systemic)**

A patient suffering from elevated IOP and/or visual field loss is treated by the oral administration of the formulation of Example 7. One or more tablets of the formulation are administered orally 1 to 4 times per day thereby reducing the IOP and/or the progression of visual field loss.

Example 11

## Method of Treatment (Intraocular or Periocular)

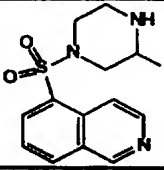
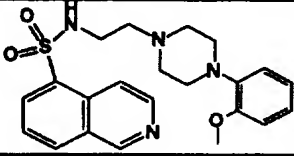
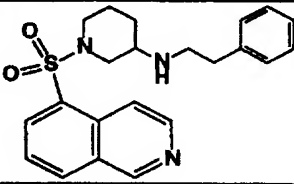
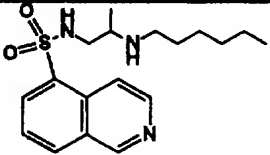
A patient suffering from elevated IOP and/or visual field loss is treated by the intravitreal or periocular administration of the formulation of Example 8. Ten to twenty-five microliters of the formulation are administered 1 time per month to the affected eye(s) thereby reducing the IOP and/or the progression of visual field loss.

Example 12

Other isoquinolinesulfonamides were topically administered to the eyes of New Zealand Albino (NZA) rabbits. The results are presented in Table 5 below.

Table 5.

## EFFECT OF OTHER ISOQUINOLINESULFONAMIDES ON IOP IN THE NZA RABBIT

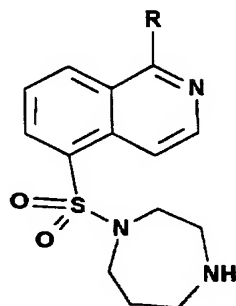
Compound	Baseline IOP (mmHg)	Percent Change from Baseline		
		1 hr	3 hr	5hr
	20.4±0.8	14.6±2.6 ↓	7.2±4.1 ↓	0.9±3.5 ↑
	19.5±0.5	7.7±4.3 ↓	14.5±0.5 ↓	0.8±2.3 ↓
	15.6±0.5	16.8±5.7 ↑	16.0±5.7 ↑	37.0±4.1 ↑
	16.2±0.3	9.9±3.5 ↓	9.4±1.9 ↓	3.3±3.8 ↑

All drugs were administered to eyes in a topical manner at a dose = 500 µg (2x25 µl). All compounds were formulated in phosphate buffered saline containing 0.01% benzalkonium chloride, and in all instances N = 7.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. An ophthalmic composition for the treatment of glaucoma, ocular hypertension, ocular ischemia and related disorders, comprising a therapeutically effective amount of a compound of the formula:



(III)

wherein R = H or OH;

and pharmaceutically acceptable salts thereof; and an ophthalmically acceptable carrier therefor.

2. The composition of claim 1, wherein the composition is a topical ophthalmic composition.

3. The composition of claim 2, wherein R = H.

4. The composition of claim 3, wherein the final composition concentration of the compound is between about 0.001 and about 10.0 wt%.

5. The composition of claim 4, wherein the final composition concentration of the compound is between about 0.01 and about 3.0 wt% and the pharmaceutically acceptable salt is hydrochloride.

6. The composition of claim 5, wherein the final composition concentration of the compound is between about 0.1 and about 2.0 wt%.

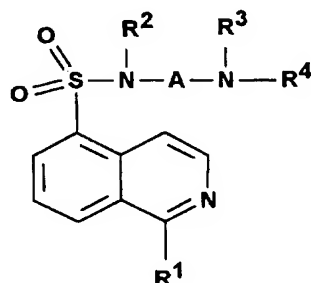
7. The composition of claim 1, wherein the composition is a topical composition further comprising at least one component selected from the group consisting of: an anionic mucomimetic polymer and a finely divided drug carrier substrate.

8. The composition of claim 7, wherein: the final composition concentration of the compound is between about 0.001 and about 10.0 wt%; both an anionic mucomimetic polymer and a finely divided drug carrier substrate are present; the final composition concentration of the anionic mucomimetic polymer is between about 0.05 and about 8.0 wt%; and the final composition concentration of the finely divided drug carrier substrate is between about 0.05 and about 10.0 wt%.

9. The composition of claim 1, wherein the composition is a topical composition further comprising at least one component selected from the group consisting of: a gelling polysaccharide and a finely divided drug carrier substrate.

10. The composition of claim 9, wherein: the final composition concentration of the compound is between about 0.001 and about 10.0 wt%; both a gelling polysaccharide and a finely divided drug carrier substrate are present; the final composition concentration of the gelling polysaccharide is between about 0.1 to about 3.0 wt%; and the final composition concentration of the finely divided drug carrier substrate is between about 0.05 and about 10.0 wt%.

11. A method of treating glaucoma, ocular hypertension, ocular ischemia and related disorders in a patient with one or more of such conditions, comprising administering to said patient a composition comprising an ophthalmically effective amount of a compound of formula:



(I)

wherein  $R^1$  represents a hydrogen atom, a chlorine atom or a hydroxyl group; and when  $R^1$  represents a hydrogen atom,

A represents an ethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms, a phenyl group or a benzyl group,

$R^2$  and  $R^3$  are directly bonded with each other, thereby forming a trimethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms, a phenyl group or a benzyl group, and

$R^4$  represents a hydrogen atom or an alkyl group having 1 to 6 carbon atoms; and

when  $R^1$  represents a chlorine atom or a hydroxyl group,

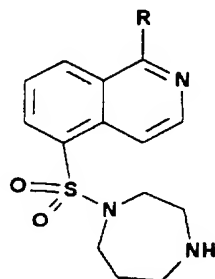
A represents an alkylene group having 2 to 6 carbon atoms, said group being unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms,

$R^2$  and  $R^3$  are not bonded with each other and each independently represent a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, or  $R^2$  and  $R^3$  are directly bonded with each other, thereby forming an ethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms or a trimethylene group unsubstituted or substituted with alkyl group having 1 to 6 carbon atoms, and

$R^4$  represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or an amidino group;

and pharmaceutically acceptable salts thereof; and an ophthalmically acceptable carrier therefore.

12. A method of treating glaucoma, ocular hypertension, ocular ischemia and related disorders in a patient with one or more of such conditions, comprising administering to said patient a composition comprising an ophthalmically effective amount of a compound of formula:



(III)

wherein  $R = H$  or  $OH$ ;

and pharmaceutically acceptable salts thereof.

13. The method of claim 12, wherein the administration of the composition is effected topically.

14. The method of claim 12, wherein  $R = H$ .

15. The method of claim 14, wherein the final composition concentration of the compound is between about 0.001 and about 10.0 wt%.



16. The method of claim 15, wherein the final composition concentration of the compound is between about 0.01 and about 3.0 wt%.

17. The method of claim 16, wherein the final composition concentration of the compound is between about 0.1 and about 2.0 wt% and the pharmaceutically acceptable salt is hydrochloride.

18. The method of claim 12, wherein the composition further comprises a sustained release component.

19. The method of claim 18, wherein the sustained release component is selected from the group consisting of: mucomimetic polymers, gelling polysaccharides, finely-divided drug carrier substrates, and combinations thereof.

# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/US 96/20197

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/55 A61K31/495 A61K31/47 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23082 A (ALCON LAB INC) 25 November 1993 see claim 10 ---	1-19
X	DATABASE WPI Section Ch, Week 9601 Derwent Publications Ltd., London, GB; Class B02, AN 96-003284 XP002030534 & JP 07 277 979 A (ASAHI KASEI KOGYO KK) , 24 October 1995 see abstract ---	1-10
Y	WO 95 15958 A (ALCON LAB INC) 15 June 1995 * p.5, 1.6 & p.6, 1.1-5; claims * --- -/-	1-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 May 1997

Date of mailing of the international search report

22.05.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

Uiber, P

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 96/20197

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DRUGS OF THE FUTURE, vol. 17, no. 12, 1992, page 1132/1133 XP000617424 "FASUDIL HYDROCHLORIDE ERIL ANTIVASOSPASTIC INTRACELLULAR CALCIUM ANTAGONIST" see the whole document -----</p>	1-19

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/US 96/20197

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323082 A	25-11-93	AU 4246793 A CA 2131101 A EP 0639986 A JP 7508030 T	13-12-93 25-11-93 01-03-95 07-09-95
WO 9515958 A	15-06-95	AU 1336895 A BR 9406080 A CA 2153979 A CN 1117292 A EP 0682664 A FI 953748 A JP 8507546 T NO 953093 A	27-06-95 06-02-96 15-06-95 21-02-96 22-11-95 07-08-95 13-08-96 09-10-95